DOCKET NO: 294986US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:	
JINDRICH RICHTER, ET AL.	:	EXAMINER: MORRIS, P.
SERIAL NO: 10/590,694	:	
FILED: AUGUST 25, 2006	:	GROUP ART UNIT: 1625
FOR: AMORPHOUS FORMS OF RISEDRONATE MONOSODIUM	:	

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, JOSEF JIRMAN, declare that:

1. I am a graduate of ORGANIC CHEMISTRY AT UNIV. OF PARDUBICE and received my PhD degree in the year 1987.
2. I have been employed by ZENTIVA a.s. for 10 years as a HEAD OF SYNTH. GR. in the field of ORGANIC SYNTHESES.
3. That I am familiar with the invention described in the above-identified U.S. Patent Application 10/590,694.
4. That the following comparative tests were show the solubility of an amorphous form of sodium risedronate both in diluted hydrochloric acid and in water as compared to

the solubility of a crystalline form of sodium risedronate, and were carried out either by me or under my direct supervision and control.

A. Dissolution of sodium risedronate in diluted hydrochloric acid

(1) 0.281 g of sodium risedronate pentahemihydrate (crystalline form A), having a water content of 12.5% (0.807 mmol), was introduced into 100 ml of stirred aqueous solution of hydrochloric acid at pH 1.1 and a temperature of 40°C. Within 30 seconds a transparent solution was formed. However, within an additional 30 seconds, a white suspension of poorly soluble risedronic acid started to precipitate and did not dissolve even upon further stirring under constant conditions.

(2) 0.250 g of sodium risedronate (amorphous form) prepared according to Example 2 of US Application 10/590,694, having a water content of 1.6% (0.807 mmol), was introduced into 100 ml of stirred aqueous solution of hydrochloric acid at pH 1.1 and a temperature of 40°C. Within less than 30 seconds a quite transparent solution was formed. It was stirred for 15 minutes more under constant conditions without any observable precipitation.

B. Dissolution of sodium risedronate in water

(1) 0.200 g of sodium risedronate pentahemihydrate (crystalline form A), having a water content of 12.5% (0.574 mmol), was suspended in 2 ml of water at 22°C. Water was added dropwise to the stirred suspension at 0.2 ml/min until a transparent solution was formed. The total volume of water required for complete dissolution of the sample was 3.5 ml.

(2) 0.200 g of sodium risedronate (amorphous form) prepared according to Example 2 of US Application 10/590,694, having a water content of 1.6% (0.645 mmol), was suspended in 2 ml of water at 22°C. stirred aqueous solution of

hydrochloric acid at pH 1.1 and a temperature of 40°C. Water was added dropwise to the stirred suspension at 0.2 ml/min until a transparent solution was formed. The total volume of water required for complete dissolution of the sample was 3.5 ml.

4. Comparison A shows that solubility in hydrochloric acid of sodium risedronate in an amorphous form of Claim 1 of US Application 10/590,694 is greater than the solubility in hydrochloric acid of crystalline sodium risedronate pentahemihydrate since, after dissolving, there does not occur any precipitation of risedronic acid in less than 20 minutes. Comparison B shows that an amorphous form of sodium risedronate of Claim 1 of US Application 10/590,694 dissolves better in water than crystalline sodium risedronate pentahemihydrate since the molar concentration pf 0.269 mol/l of an amorphous form of sodium risedronate of Claim 1 of US Application 10/590,694 can be more readily achieved. For the crystalline form, only a concentration of 0.164 mol/l was achieved upon complete dissolution under the same conditions.
5. The undersigned declares further that all statements made herein are known or believed to be true; and further that these statements were made with made with the knowledge that willful false statements made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Signature

Date 8. 9. 2008

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